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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,288	05/15/2006	Xianghui Yi	34569-716.831	7077

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EXAMINER	
RAO, SAVITHA M	

ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
08/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,288	YI, XIANGHUI	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-25* is/are pending in the application.

4a) Of the above claim(s) *7-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-6 and 11-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/15/2008, 09/19/2007, 07/10/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 4-25 are pending and are subject of this office action.

Receipt is acknowledged of a preliminary amendment filed on 07/10/2008 in which claims 1-3 were cancelled, claims 4-6 was amended, claim 7-10 were withdrawn and new claims 11-25 were added.

Claims under consideration in the instant office action are claims 4-6 and 11-25.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed on 05/15/2008, 09/19/2007 and 07/10/2008. The Examiner has considered the reference cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Foreign documents citation # 2 in the IDS submitted on 07/10/2008 and foreign documents citation # 28-31 in IDS submitted on 09/19/2007 has been lined out since the no English translations of these documents were provided.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-6) the reply filed on 07/10/2008 is acknowledged. An amendment filed on 07/10/2008 with the response had claims 1-3 cancelled, claims 4-6 amended, claim 7-10 withdrawn and new claims 11-25 were added. Claims under consideration in the instant office action are claims 4-6, 11-25

The requirement is deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The claimed invention in instant claims 14-16, 18 and 20-22 is directed to non-statutory subject matter. Instant claims 14-16, 18, and 20-22 are non-statutory because these are product claims which also require the method step of "is administered". Such combining of product and process limitations is non-statutory subject matter and are therefore rejected under 35 U.S. C. 101.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

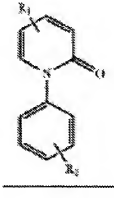
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 4-6 and 11-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin (US 5716632) in view of Gadekar (US 3839346) and Margolin (EP 1069898, provided in the IDS, referred in this rejection as Margolin (EP)

Instant claim 4-6 and 11-25 is drawn towards a pharmaceutical composition comprising a pharmaceutically acceptable carrier and effective amount of the compound of formula 1

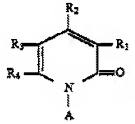


Formula (I)

Where R1 is methyl at position 5 and R2 is hydroxy at position 4 (instant claims 11 and 12), wherein the dosage form is in the form of a tablet, capsule, ampoule or a pill (instant claim 6), composition comprises pharmaceutically acceptable carriers or excepients (instant claims 13, 23-25), where in the composition comprise 0.01-99% or 0.1-90% of the compound of formula I (instant claims 5 and 19), wherein the composition is administered orally , parenterally or externally (instant claims 14-18) and wherein the composition is administered at

a dose of 0.25-1000 mg/kg or 2-80 mg/kg animal body weight administered in 2-4 separate dosage per day or in the form of slow release (instant claims 20-22).

Margolin teaches drugs having pharmacological properties which are useful in the medic8inal therapy of fibrotic disease, such drugs including as active ingredients one or more N-substituted 2-(1H) pyridone(s) and/or N-substituted 3-(1H) pyridones as active anti-fibrotic ingredients (abstract, col.1,lines 19-25). Margolin teaches that the use of pirfenidone (5-methyl-1phenyl-2(1H)pyridine) in the reparation and prevention of fibrotic lesions.(col.1,lines 49-53). Margolin teaches N-substituted 3-(1H) pyridones useful in his inventions and exemplifies compounds of formula (col. 11, line 20-33)



where: R2 or R3=alkyl group or hydrogen, as above; A is phenyl, thienyl, etc., or other aryl. R1 and R4 are hydrogen.
Examples of the 2 and 3 pyridones include:
5-Methyl-1-(3-nitrophenyl-2)-(1H) pyridone
5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone

The only difference between the instantly claimed compound and the5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone taught by Margolin is the substitution in the phenyl ring attached to the pyridone moiety, Instead of the methoxy substituent at position 4 of the phenyl ring taught by Margolin, instant

application recites an hydroxy substitution. It has been determined by the court **that hydrogen and methyl are deemed obvious variants**, *In-re Wood* 199 USPQ 137. Accordingly, it would have been obvious for one of ordinary skill in the art to substitute hydrogen for the methyl group of the methoxy function attached at the 4' position of the phenyl group in the compound taught above to obtain a hydroxy derivative.

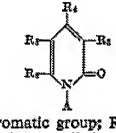
Additionally Margolin teaches examples of medical preparations of the compound pirfenidone useful in his preparations which include (1) capsules (2) tablets (3) powders (4) granules (5) syrups (6) injections (intravenous, intramuscular or drip administration. (7) cream (8) ointment (9) inhalation (10) eye drop (11) suppositories (12) pills, etc. and indicates that the preparations preferred among these are the capsules, injections cream and ointments (col.10, lines 36-45). Margolin teaches capsules comprising 800 mg, 1600 mg or 1600 mg of pirfenidone (col. 10, line 49-50) and hydrophilic ointment containing 5-10% pirfenidone (col. 10, line 54). Margolin additionally teaches that the average oral dosage of pirfenidone for anti-fibrotic activity in humans is 3600 mg/day with a range of from about 2400 mg to about 4800 mg/day and that the administration may be in divided dosage, for example 1200 milligrams three times per day. (col. 10, lines 56-60). Margolin teaches the effective dosages and rates of application of the compositions of his invention comprising other N-substituted 3 (1H) pyridones to be effective in the range from about one quarter to about twice the dosages given above for pirfenidone (col. 12, lines 20-24) and the composition being administered to a patient at rate of from about 5 mg/kg of body weight per

day to about 300 mg/kg of body weight per day(col.12, claim 1). Additionally Margolin teaches that compositions of his invention may be administered in forms consisting of capsules, tablets, powders, granules, syrups, injectable fluids, pills, cream, ointment, inhalable fluids, eye drops and suppositories (col. 12, lines 25-28, claim 9, 12). Accordingly, Margolin provides one of ordinary skill in the art motivation to synthesize N-substituted pyridones with different substitution on the phenyl group and formulate a pharmaceutical composition comprising those derivatives.

What Margolin does not teach does the composition comprise one are more pharmaceutically acceptable carriers or excepients.

This deficiency is taught by Gadekar and Margolin (EP)

Gadekar teaches Novel analgesic compositions containing as the active ingredient the4 compound 5-methyl-1-phenyl-2(1-H) pyridone (abstract). Gadekar also describes methods of making related pyridones having the formula



II

wherein A is an aromatic group; R_3, R_4, R_5 and R_6 are individually each hydrogen, alkyl, aryl or substituted aryl;

(col. 3, lines 14-27) and in example 3 Gadekar teaches the synthesis of 5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridone taught by Margolin above (col.5, lines 69-75).

Gadekar teaches pharmaceutical composition of 5-methyl-1-phenyl-2(1-H)pyridone formulated together with a pharmaceutically acceptable carrier, solid carrier, diluent or a gaseous carrier to provide pharmaceutical compositions in forms suitable for therapeutic administration (col.2, lines 42-49). Gadekar teaches that the solid carriers are useful in formulation of dosage forms such as pills, tablets , powders or cachets for immediate or sustained release and may include flavors or therapeutic adjuvtants , the liquid carrier can provide flavorful vehicle for oral administration or may be adjusted to tonicity to be used in injectable preparations.(col.2, lines 50-60). Additionally, Gadekar teaches that the standard pharmaceutically acceptable carriers normally used in such pharmaceutical formulations can be utilized in formulating the aforementioned compositions of his invention (col.3, lines 9-13) and in example 30 provides a formulation comprising talc an corn starch as carriers, along with other excepients (col.8, lines 16-31). Accordingly Gadekar provide one of ordinary skill in the art motivation to formulate compositions of N-substituted pyridine derivatives with different types of carriers based on the final dosage form of the formulation.

Margolin (EP) teaches antiseptic compositions and more particularly, an ointment, cream, or foam containing pirfenidone and and/or related compounds, for disinfecting the skin [0001]. Margolin (EP) teaches hydrophilic ointment compositions comprising propylene glycol, stearyl alcohol and white petrolatum (example 7, ([0044) and a vanishing cream formulation of pirfenidone comprising

stearic acid, isopropyl myristate, mineral oil, stearyl alcohol, propylene glycol and sterile distilled water (example 8, [0045]).

Accordingly Gadekar and Margolin (EP) provides motivation to one of ordinary skill in the art to prepare compositions of compounds structurally similar to pirfenidone using either solid vehicles such as starch and talc or liquid vehicles such as sterile water, mineral oil and other excepients based on the final intended applications method (oral, parenteral or topical).

The differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. It would have been *prima facie* obvious to the skilled artisan to combine the teachings Margolin and Gadekar to prepare 5-methyl-1-phenyl-2(lH) pyridine with different substituents at the 4' position of the phenyl moiety. A compound with no phenyl substitution (5-methyl-1-phenyl-2(1-H or pirfenidone) and the one with methoxy substituent on position 4' of the phenyl ring (5-Methyl-1-(4'-methoxyphenyl)-2-(1H) pyridine) are already taught in the art and pharmaceutical compositions of these compounds and the fact that they possess anti-fibrotic activity has already been taught. In view of the close structural similarity between the claimed compound in the instant pharmaceutical composition and the compound taught by both Margolin and Gadekar, one of ordinary skilled in the art would have been motivated to formulate instantly claimed compositions, in the expectation that the composition would possess similar anti-fibrotic activity.

An ordinarily skilled artisan will be able to develop such a dosage form with a reasonable expectation of success based on the state of the art at the time of invention in order to provide a better range of anti-fibrotic compounds for treatment of fibrosis.

Conclusion

Claims 4-6 and 11-25 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service

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/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614